NEWBORN SCREENING
NEWS

The California Newborn Screening Program Fall 2001

Supplemental Screening for Multiple Metabolic Disorders

MS/MS Research Project

Background

"The introduction of Tandem Mass Spectrometry (MS/MS) in the 1990's for population-based newborn screening has enabled healthcare providers to detect an increased number of metabolic disorders in a single process using dried blood spot specimens routinely collected for newborn screening."[1] MS/MS allows for screening of multiple metabolic disorders using a single analytical run. With this technology there is the potential to test for a wide array of metabolic disorders, including amino acid disorders, organic acidemias, and fatty acid oxidation disorders. Because the technology can detect these disorders (approximately 30 total) within 1 to 2 minutes, the system can handle the large numbers of specimens required in newborn screening. For some of the disorders identifiable via MS/MS, such as medium chain acyl-CoA dehydrogenase deficiency (MCADD), early detection and treatment can result in substantial improvements in health outcomes (i.e., prevention of mortality and improvement of quality of life). Several states have already expanded, or are in the process of expanding, their newborn screening program to add these disorders.

The California Newborn Screening Program, which has been in existence since 1980, currently tests for PKU, galactosemia, primary congenital hypothyroidism, sickle cell disease and other hemoglobinopathies. On September 28, 2000, Governor Gray Davis signed into law Assembly Bill 2427 (Kuehl) which provides for updating and expanding the newborn screening program in California. The law took effect on January 1, 2001. AB 2427 requires the Department of Health Services to investigate the feasibility of establishing a new and broader testing program, including development and evaluation of expanded genetic disease testing utilizing Tandem Mass Spectrometry. In response, the Department plans to expand screening as a part of a research (pilot) project.

The Genetic Disease Branch (GDB) of the DHS has been actively planning for implementation of the project for over a year. Meetings of metabolic and laboratory experts from across the state were held in October, 2000 and May, 2001 to develop recommendations regarding the specific disorders to be included in the initial phase and to discuss the implementation process. The research proposal for the project has been reviewed and approved by the State Health and Human Services Agency's Committee for The Protection of Human Subjects.

This study is being conducted in part to determine which of the disorders identifiable via MS/MS meet the criteria for inclusion in California's mandatory Newborn Screening Program, i.e., which of the unusual results have clinical significance and what warrants reporting. Initially all "interesting" or "unusual" results will be reported to the pediatric care provider, then to a metabolic specialist for evaluation. Treatment and outcome data will also be collected on all newborns referred to Metabolic Centers for follow-up.

The NBS MS/MS Research Project

The actual start date will be announced at least 1 month prior to implementation. The estimated duration of the supplemental testing is 12-18 months. Participation in the study will be voluntary and informed consent will be obtained for both the testing of specimens and for release of medical information for newborns referred to metabolic centers. There will be no additional fee charged

[1] Centers for Disease Control and Prevention. Using Tandem Mass Spectrometry for Metabolic Disease Screening Among Newborns: A Report of the Workgroup—Georgia, 2000. MMWR Morb Mortal Wkly Rep., Recommendations and Reports April 13, 2001:50:1

for participation in the supplemental screening and no additional blood will be needed. National experience to date in MS/MS screening using a full panel of acylcarnitines and amino acid analyses has resulted in a detection rate between 1:4,000 to 1:5,000[2] (Chace et al). Based on the annual California birth rate and the acceptance rate reported by other states that have offered MS/MS supplemental screening, we project about 400,000 newborns participating in the pilot project and detecting an additional 40-60 newborns with clinically significant metabolic disorders not included in the current California mandatory newborn screening program.

MS/MS Research Project Screening Process

Information on the mandatory newborn screening program as well as the supplemental screening via the pilot project will be provided to parents by prenatal care providers and hospital staff. Written verification of informed consent will be obtained by hospitals and birthing centers using a form provided by the State (included in the Newborn Screening Program booklet, entitled *Important Information for Parents About the Newborn Screening Test*).

Specimen collection, handling and transport will occur in the same manner as the current mandatory screening. Hospital staff will complete the demographic information on the newborn screening Test Request Form (TRF), also known as the Newborn Screening Specimen Collection Form. The blood specimen will be collected from the newborn's heel and dropped onto the five (5) blood spots on the filter paper attached to the TRF and allowed to dry. A separate collection form for this project will not be necessary. The hospital staff will indicate whether the newborn is to be enrolled in the supplemental study by affixing color-coded stickers (indicating "YES" or "NO") to both the demographic portion of the form and to the filter paper. They will then send the TRF with the dried blood spots to their assigned Newborn and Prenatal Screening (NAPS) Laboratories.

The NAPS Laboratories will conduct the mandatory testing as usual on all specimens deemed adequate. Data entry of demographic information will include the decision to participate in the voluntary supplemental screening. Data will be transmitted to GDB as usual. Upon completion of mandatory testing, all filter papers will be sent to the MS/MS testing laboratory, which is on site at the Genetic Disease Laboratory Section in Berkeley. The testing laboratory will run supplemental testing *only* on adequate specimens where informed consent has been obtained and the "YES" sticker is affixed to the form. The results of the MS/MS testing will be reviewed and released by the laboratory and then sent electronically to the Genetic Disease Branch.

Written results will be released only for specimens with unusual findings. These will be sent to the newborn's physician and the hospital/collection site as listed on the TRF. For all unusual results the primary care provider will be contacted immediately via telephone by the MS/MS Project Clinical Follow-up Coordinator and the newborn referred to one of the California Children's Services (CCS)-approved Metabolic Centers for confirmation of diagnosis and initiation of treatment, if warranted.

If there is a family history of one of the conditions or other special concerns the family should be offered information on the option of obtaining supplemental testing outside of, or in addition to, the research study e.g., optional supplemental screening is offered for a fee by Neo Gen Screening, Inc. (Bridgeville, Pennsylvania http://www.neogenscreening.com) and Baylor University Medical Center (Dallas,Texas, http://www.baylordallas.edu).

The evaluation component of the project will consist of: the development and maintenance of the supplemental screening database, ongoing monitoring of all aspects of the pilot project and outcome data, including analysis of laboratory data and results, collection and analysis of follow-up clinical data, collection and analysis of cost and treatment data, and assessment of which disorders would be appropriate for inclusion in the mandatory screening program. Feedback will be solicited from parents, primary care providers, CCS Centers, state staff and contractors.

Informed Consent

During the research project written documentation of informed consent will be required for the voluntary supplemental (MS/MS research/pilot project) testing. To help facilitate this process the information about the mandatory Newborn Screening Program and the voluntary supplemental testing have been combined into one booklet. The informed consent form, which needs to be signed at the hospital, is included in the booklet. Copies of these booklets will be distributed to hospitals and prenatal care providers one month prior to the project start date.

[2] Enhancement of Newborn Metabolic Disease Screening with the Implementation of Tandem Mass Spectrometry: Proceedings of a 2000 Workshop

Key Points About the Voluntary Supplemental Research Project:

- There is no additional cost for the voluntary supplemental screening test.
- No additional blood will be taken from the newborn.
- Knowledge gained from this project will be used to improve screening for newborns and families.
- There could be some benefit to families who participate e.g., early detection and treatment for newborns with one of the disorders.
- Because this is a research study, written results will only be provided on specimens with unusual results. **If a specimen is inadequate the supplemental testing will not be run and parents will not be notified or offered retesting through the program.**

Many current participants in the mandatory Newborn Screening Program will have the following new and/or expanded roles in this project:

Role of Prenatal Care Providers/Birth Attendants:

Prenatal care providers are required by law to distribute a copy of the informational material, *Important Information for Parents About the Newborn Screening Test*, which describes the mandatory newborn screening program.[3] Prenatal care providers will need to make sure that all women who are due to deliver during the pilot period receive a copy of the revised Newborn Screening Program booklet which contains information regarding the research project and have all of their questions regarding the MS/MS research project answered.

Birth attendants will be responsible for ensuring that women who did not obtain prenatal care receive information on both the mandatory Newborn Screening Program and the MS/MS research project prior to specimen collection. They will need to verify the mother's understanding of the project and offer the option of the supplemental screening.

Role of Hospitals/Birthing Centers

Written verification of informed consent will be obtained by hospitals and birthing centers using the form included in the Newborn Screening Program booklet. Hospital staff will indicate whether the newborn is to be enrolled in the MS/MS research study by affixing color-coded stickers (indicating "YES" or "NO") on the newborn screening Test Request Form (filter paper and demographic sheet). **The MS/MS research project testing will only be done on initial adequate specimens with a "YES" sticker on the filter paper.** Hospital staff should assure correct and accurate pediatric care provider information on the form and send the 5-blood-spot specimens on the Test Request Form via the usual Newborn Screening route to the NAPS Labs for processing.

Role of Pediatric Care Providers

Pediatric Care Providers should be knowledgeable about the program and available to answer questions and provide additional information to parents and hospital staff. They will need to refer patients with unusual screening results to approved CCS Metabolic Center specialists. As always, providers should not rule out metabolic disorders solely based on newborn screening results. Any signs and symptoms of potential disorders should be followed up and any diagnosed cases reported to the GDB. It is also essential that they assure that hospitals which are entering their names and addresses on the Test Request Form have accurate and current information.

Because this is a research study, written results of the MS/MS research project will only be provided on specimens with unusual findings. In these situations, the Pediatric Care Provider will be contacted via telephone by the MS/MS Follow-up Coordinator and the newborn referred to one of the California Children's Services (CCS)-approved Metabolic Centers for confirmation of diagnosis and initiation of treatment.

Role of Metabolic Centers

The Metabolic Medical Specialists will be available to answer questions about the program, the MS/MS technology and the disorders being tested. They will also be asked to consult and participate in development and evaluation of the project.

The Metabolic Centers will make the arrangements for confirmatory testing and develop the diagnostic and treatment plan, which will then be forwarded to the primary care provider and the Genetic Disease Branch. Based upon experience of the research project and input from metabolic specialists, follow-up guidelines will be developed.

Role of Local/County Health Departments

Health Departments may be asked to locate families in their area for screening or for follow up of unusual results.

Role of NBS Area Service Center Staff

Area Service Center Staff will contact hospitals in their regions to improve reporting of correct information on the TRF and to reinforce information provided by the State

[3] California Code of Regulations, Title 17, Subchapter 9 Heritable Diseases, Sections 6500-6508

regarding the project. They will follow up with hospitals not offering the MS/MS research project testing or who have only a small percent of parents agreeing to participate. They may be asked to assist the MS/MS Project Follow-up Coordinator in locating a family or in dealing with a provider in their region.

Providers or patients who have questions can call the California Department of Health Services, Newborn Screening Program MS/MS Research Project Staff at (866) 718-7915 toll free for additional information.

Changes in Billing for The Newborn Screening Test

In addition to authorizing the tandem mass spectrometry research project, AB 2427 requires the Genetic Disease Branch to dramatically change the manner in which newborn screening test panels are billed. Since 1980, GDB has billed hospitals and other newborn screening providers. The providers, in turn, would bill patients, their insurance companies, and Medi-Cal. AB 2427 requires that as of July 1, 2001 GDB stop billing hospitals and other newborn screening providers. GDB will initiate direct billing for newborn screening:

1. **Kaiser Permanente Health Plan** will be billed directly for their patients. Kaiser patients should not receive a bill for newborn screening from GDB.

2. **Medi-Cal** patients will be billed directly to Medi-Cal. GDB has added a field to the demographic portion of the Newborn Screening Test Request Form (NBS-TRF) for the mother's Medi-Cal number. GDB will use the hospital-reported Medi-Cal number to bill Medi-Cal. Those patients whose valid Medi-Cal number is reported by the hospital will not receive a bill for newborn screening from GDB.

3. The mothers of all other patients will receive a bill for newborn screening from GDB. Accompanying the bill will be an insurance information form. Mothers will have two choices. They can pay GDB directly and then submit a claim to their insurance company for reimbursement, or they can complete the insurance information form and return it to GDB. The Genetic Disease Branch will, in turn, bill their insurance company. Included with the bill, will be the telephone number that mothers can call with questions about their bill for newborn screening.

The Genetic Disease Branch anticipates sending out its first bills for newborn screening in mid-September. This means that patients whose babies were born and tested in July and August won't receive a bill for several months after the baby's birth. Newborns tested in July, August and September will be billed $42.00 for newborn screening. We anticipate that the cost of newborn screening will rise, for the first time since 1994, to $55.00 on or about October 1, 2001.

Newborn Screening Area Service Centers (NBS-ASCs)

CHO	
Children's Hospital Oakland	(510) 428-3127
VCH	
Valley Children's Hospital	(559) 353-6416
UCLA	
UCLA Medical Center	(310) 826-4458
Harbor/UCLA	
Harbor/UCLA Medical Center	(310) 222-3751
SDICDSI	
San Diego-Imperial Counties Developmental Services, Inc.	(858) 576-2975
Kaiser N	
Kaiser Permanente, Northern CA	(510) 752-6192
Kaiser S	
Kaiser Permanente, Southern CA	(626) 564-3322

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